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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/729,441	12/08/2003	Rajeeva Singh	A8689	3309

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EXAMINER	
DUFFY, BRADLEY	
ART UNIT	**PAPER NUMBER**
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/729,441	SINGH ET AL.	
	Examiner	Art Unit	
	Brad Duffy	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-22 and 24-37* is/are pending in the application.

4a) Of the above claim(s) *20,21,25,28,29,35 and 36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-19,22,24,26,27,30-34 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. The amendment filed April 16, 2007, is acknowledged and has been entered in part. The amendment to the claims section was non-compliant with the requirements set forth under 37 C.F.R. § 1.121 and has not been entered.

2. The amendment filed July 5, 2007, is acknowledged and has been entered. Claims 4-5 and 23 have been cancelled. Claims 1, 2, 7-17, 24, 32-34 have been amended. Claims 35-37 have been newly added.

3. The declaration under 37 C.F.R. § 1.132 by Rajeeva Singh, Daniel J. Tavares, and Nancy E. Dagdigian filed April 16, 2007, is acknowledged and has been entered.

4. The declaration under 37 C.F.R. § 1.132 by Rajeeva Singh and Nancy E. Dagdigian filed August 24, 2007, is acknowledged. Because the copy of the declaration presently made of record is not executed, it has not been entered.

5. Claims 1-3, 6-22 and 24-37 are pending in the application.

6. Claims 20, 21, 25, 28, 29, 35 and 36 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Notably, new claims 35 and 36 are drawn to the non-elected invention of Group III and are therefore withdrawn.

7. Claims 1-3, 6-19, 22, 24, 26, 27, 30-34 and 37 are under examination.

8. The following Office action contains NEW GROUNDS of objection and rejection necessitated by amendment.

Priority

9. Applicant's claim under 35 USC §§ 119 and/or 120 for benefit of the earlier filing date of the 10/170,390, filed June 14, 2002, is acknowledged.

However, claims 1-3, 6-19, 22, 24-27, 30-34 and 37 do not properly benefit under 35 U.S.C. §§ 119 and/or 120 by the earlier filing dates of the priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure.

To receive benefit of the earlier filing date under 35 USC §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

In addition, claims 2, 17, 30, and 32-34 do not properly benefit by the earlier filing because, although the document describes a composition comprising an antibody and a second agent, it does not describe such a composition comprising any of the agents of claim 2, nor does it describe such a composition in a kit, *per se*.

Accordingly, the effective filing date of the claims is deemed the filing date of the instant application, namely December 8, 2003[1].

Grounds of Objection and Rejection Withdrawn

10. Unless specifically reiterated below, Applicant's amendment and/or arguments filed April 16, 2007 and July 5, 2007, have obviated or rendered moot

[1] The Office action mailed November 6, 2006 inadvertently listed the incorrect filing date of the instant application as US Application was filed December 8, 2003

the grounds of objection and rejection set forth in the previous Office action mailed November 6, 2006.

Response to the Declaration under 37 C.F.R. § 1.132

11. The declarations under 37 C.F.R. § 1.132 filed April 16, 2007 and August 24, 2007 are insufficient to overcome the rejection of claims 1-3, 5-19, 22, 24, 26, 27, 30, 31 and 37 under 35 U.S.C. 102(a) as being anticipated by Maloney et al (Cancer Research 63:5073-5083, August 15, 2003) as set forth in the last Office action for the following reasons:

As noted by the Examiner during the interview of August 22, 2007, with Applicant's representative, Mr. William Simmons, the declaration filed April 16, 2007, incorrectly states that inventor Tavares was a co-author of the Maloney paper; the reference by Maloney et al. did not list inventor Tavares as a co-author.

In light of this factual error, Applicant has since submitted a second declaration by Rajeeva Singh and Nancy E. Dagdigian filed August 24, 2007; however, because inventor Singh did not execute the copy of declaration that has been submitted, it cannot be entered or considered sufficient to overcome this rejection (see 37 CFR § 1.63).

Nevertheless, as a courtesy, Applicant is informed that if an executed copy of the declaration were submitted, the declaration would be sufficient to establish that the Maloney et al. reference is not available as prior art under 35 U.S.C. § 102(a).

Grounds of Objection Maintained

Specification

12. The objection to the specification, because the use of improperly demarcated trademarks, is maintained. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Although it appears that Applicant has made a *bona fide* attempt to resolve this issue by appropriately amending the specification, an additional example of an improperly demarcated trademark appearing in the specification is noted, namely Iressa™; see, e.g., paragraph [32], page 11 of the specification.

Again, appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at <http://www.uspto.gov/web/menu/search.html>.

Claims

13. The objection to claims 22, 30, 31 and 34, as being drawn in the alternative to the non-elected invention of Group III, is maintained. Applicant has requested rejoinder of the non-elected claims of Group III, upon allowance of product claims in the response to the restriction requirement filed September 9, 2006.

Grounds of Rejection Maintained

Claim Rejections - 35 USC § 112

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. The rejection of Claims 1-3, 6-19, 22, 24, 26, 27, 30-34 and 37 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

At page 32 of the amendment filed April 16, 2007, Applicant has traversed the propriety of this ground of rejection.

Applicant's arguments have been carefully considered but are not found persuasive for the following reasons:

Again, the considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

As amended, the claims are directed to compositions and methods of using said compositions, wherein the compositions comprise an antibody or an epitope-binding fragment thereof, wherein said antibody of said fragment specifically binds to insulin-like growth factor-I receptor, and wherein said antibody has the same binding specificity as murine antibody EM164 and a therapeutic agent. Claim 7 limits the antibody to an antibody that comprises a heavy chain variable region and a light chain variable region wherein the heavy chain variable region comprises the complementary determining regions comprising the amino acid sequences of SEQ ID NO:1-3. Claim 8 limits the antibody to an antibody that comprises at least one heavy chain variable region and at least one light chain variable region wherein the heavy chain variable region comprises the complementary determining regions comprising the amino acid sequences of SEQ ID NO:1-3 and wherein the light chain variable region comprises the complementary determining regions comprising the amino acid sequences of SEQ ID NO:4-6. Claims 9-11 limit the antibodies to a antibody comprising a heavy chain variable region that has 90%, 95% or 100% sequence identity to SEQ ID NO:7. Claims 12-14 limit the antibodies to a antibody comprising a light chain variable region that has 90%, 95% or 100% sequence

identity to SEQ ID NO:8. Claim 15 limits the antibodies to a antibody comprising a light chain variable region selected from: SEQ ID NO;9, SEQ ID NO:10, SEQ ID NO:11 or SEQ ID NO:12. Claim 16 limits the antibodies to a antibody comprising a heavy chain variable region comprising SEQ ID NO:13.

While, antibodies having the same binding specificity as murine antibody EM164 are not expressly defined in the specification, they are being interpreted in light of the disclosure of original claim 1, which recites that such antibodies include functional equivalents and variants of the murine antibody EM164 with mutations, deletions or insertions. Furthermore the specification discloses at page 17 that:

> "The primary amino acid and DNA sequences of antibody EM164 light and heavy chains, and of humanized versions, are disclosed herein. However, the scope of the present invention is not limited to antibodies and fragments comprising these sequences" and
> "The CDRs of antibody EM 164 are identified by modeling and their molecular structures have been predicted. Again, while the CDRs are important for epitope recognition, they are not essential to the antibodies and fragments of the invention".

Thus, the claims are still broadly, but reasonably interpreted as encompassing an extremely large genus of structurally and functionally diverse functional equivalents or variants of antibodies that do not necessarily retain any particularly identifying structural feature of the EM164 antibody that correlates with the ability of these functional equivalents or variants to bind insulin-like growth factor-I receptor.

Therefore, as set forth in the preceding Office action at page 10, "while the specification describes antibodies that specifically bind insulin-like growth factor-I receptor or epitope-binding antibody fragments of insulin-like growth factor-I receptor, (e.g., EM164), none are representative of the genus, as a whole, since there is no disclosure of a correlation between any one particularly identifying (i.e., substantial) structural feature, which is shared by these antibodies and other

functional equivalents or variants of antibodies to which the claims are directed, and any one functional feature also shared by at least most of the genus.

Consequently, the skilled artisan could not immediately envision, recognize or distinguish at least most of the members of the genus of functional equivalents or variants of antibodies to which the claims are directed; and therefore the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed".

Notably, while the specification does teach that the murine antibody EM164 comprises a heavy chain variable region comprising a CDR1 consisting of SEQ ID NO:1, a CDR2 consisting of SEQ ID NO:2, a CDR3 consisting of SEQ ID NO:3 and a light chain variable region comprising a CDR1 consisting of SEQ ID NO:4, a CDR2 consisting of SEQ ID NO:5, a CDR3 consisting of SEQ ID NO:6, the claims are not limited to antibodies comprising these CDRs consisting of amino acid sequences of SEQ ID Nos:1-6 in the proper context of variable region frameworks. Thus, for example, claim 8 is included in this rejection even though it is limited to a heavy chain variable region comprising the complementary determining regions comprising the amino acid sequences of SEQ ID NO:1-3 and a the light chain variable region comprises the complementary determining regions comprising the amino acid sequences of SEQ ID NO:4-6 because it does not recite that the CDRs consist of these amino acids sequences and one of skill in the art would not be able to immediately envision or recognize which other functional equivalents or variants containing CDRs with additional amino acids would bind insulin-like growth factor-I receptor because adding amino acids to the CDRs of an antibody would alter the three-dimensional structure of the resulting antibody.

Therefore, Applicant's argument in the response filed April 16, 2007 pages 32 and 33, bridging paragraph and paragraph 2(b) on page 33 that the amendment of the claims overcomes this rejection is not persuasive.

Additionally, at page 33 Applicant asserts that heavy chain variable regions with 90-95% identify to the heavy chain variable region of SEQ ID NO:7 or that light chain variable regions with 90-95% identify to the light chain variable region of SEQ ID NO:8 are adequately described.

In response, as set forth at page 11 of the preceding Office action and as set forth above the specification only adequately describes antibodies comprising the six CDRs of monoclonal antibody EM1646 in the proper context of variable region frameworks. Furthermore, the specification does not disclose any additions, deletions or mutations made in these CDRs wherein the antibody retains binding to insulin-like growth factor-I receptor. However, the genus encompasses any mutations, insertions or deletions that result in a heavy chain variable region with 90-95% identify to SEQ ID NO:7 or a light chain variable region with 90-95% identify to SEQ ID NO:8. Therefore, while Applicant argues that the specification teaches 4 homologues of the light chain and one homologue of the heavy chain, these species are not representative of the genera of heavy chain variable regions with 90-95% identify to SEQ ID NO:7 or a light chain variable region with 90-95% identify to SEQ ID NO:8 as each of these homologues comprise the CDRs of the parent murine monoclonal EM164 antibody. Thus one of skill in the art would not be able to immediately envision or recognize which mutations, insertions or deletions that result in a heavy chain variable region with 90-95% identify to SEQ ID NO:7 or a light chain variable region with 90-95% identify to SEQ ID NO:8 would retain binding to comprising a heavy chain variable region with 90-95% identify to the heavy chain variable region of SEQ ID NO:7 would bind insulin-like growth factor-I receptor and thus the claimed antibodies are not adequately described.

It is aptly noted that the Federal Circuit has decided that a generic statement that defines a genus of substances by *only* their functional activity, i.e., the ability to bind a cancer cell and inhibit its growth, does not provide an adequate written description of the genus. See *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997). The Court indicated that

while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

Although *Lilly* related to claims drawn to genetic material, the statute applies to all types of inventions. "Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1984 (CAFC 2004).

Accordingly, after careful and complete consideration, contrary to Applicant's arguments, for these reasons and as explained more fully in the Office action mailed November 6, 2006, the specification as filed does not adequately describe the antibodies to which the claims are directed and this rejection is maintained.

16. The rejection of Claims 2, 17, 30, and 32-34 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is maintained. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a NEW MATTER rejection.

At page 36 of the amendment filed April 16, 2007, Applicant has traversed

this ground of rejection.

Applicant's arguments have been carefully considered and while found persuasive with respect to therapeutic agents interferon alpha-2a and vincristine were are not found persuasive with respect to therapeutic agents thalidomide, carmustine, pamidronate, prednisone, erythropoietin and bisohosphonate for the following reasons:

Applicant submits that "MPEP §2163.07(b) states that information incorporated by reference is as much a part of the application as filed as if the text was repeated in the application, and should be treated as part of the text of the application as filed" and that the specification has been amended with the relevant portions of DeVita et al that describe the therapeutic agents thalidomide, carmustine, pamidronate, prednisone, erythropoietin and bisohosphonate.

In response, since the specification did not particularly point to the relevant portions of DeVita et al that Applicant is attempting to introduce into the specification, this amendment is deemed to introduce new matter to the specification (see new matter objection to the specification below) and therefore the amendment to the specification with the relevant portions of DeVita et al is not sufficient to overcome this rejection.

Additionally MPEP §2163.07(b) points to 37 CFR 1.57 and MPEP § 608.01(p) for Office policy regarding incorporation by reference.

According to M.P.E.P. 608.01(p):

> Mere reference to another application, patent, or publication is not an incorporation of anything therein into the application containing such reference for the purpose of the disclosure required by 35 U.S.C. 112, first paragraph. *In re de Seversky*, 474 F.2d 671, 177 USPQ 144 (CCPA 1973).
>
> Particular attention should be directed to specific portions of the referenced document where the subject matter being incorporated may be found.

Additionally, with regard to incorporation by reference, the Federal Circuit in deciding *Advanced Display Systems Inc. v. Kent State University,* 54 USPQ2d 1673 (CA FC), has further opined:

> Incorporation by reference provides a method for integrating material from various documents into a host document--a patent or printed publication in an anticipation determination--by citing such material in a manner that makes clear that the material is effectively part of the host document as if it were explicitly contained therein. *See General Elec. Co. v. Brenner*, 407 F.2d 1258, 1261-62, 159 USPQ 335, 337 (D.C. Cir. 1968); *In re Lund*, 376 F.2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents. *See In re Seversky,* 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which is incorporated and where it is to be found"); *In re Saunders*, 444 F.2d 599, 602-03, 170 USPQ 213, 216-17 (CCPA 1971) (reasoning that a rejection for anticipation is appropriate only if one reference "expressly incorporates a particular part" of another reference); *National Latex Prods. Co. v. Sun Rubber Co.*, 274 F.2d 224, 230, 123 USPQ 279, 283 (6th Cir. 1959) (requiring a specific reference to material in an earlier application in order have that material considered part of a later application); *cf. Lund*, 376 F.2d at 989, 153 USPQ at 631 (holding that a one sentence reference to an abandoned application is not sufficient to incorporate material from the abandoned application into a new application). Whether and to what extent material has been incorporated by reference into a host document is a question of law. *See Quaker City Gear Works, Inc. v. Skil Corp.*, 747 F.2d 1446, 1453-54, 223 USPQ 1161, 1166 (Fed. Cir. 1984) (reasoning that whether a document is incorporated by reference into a patent presents a question of law when determining enablement). *Id.* at 1679-1680.
>
> [Thus] the standard of one reasonably skilled in the art should be used to determine whether the host document describes the material to be incorporated by reference with sufficient particularity. *Id.* at 1680.

Thus the mere reference to Devita et al would not lead one of skill in the art to understand that Applcaint intended to include the therapeutic agents thalidomide, carmustine, pamidronate, prednisone, erythropoietin and bisohosphonate.

Thus, after a careful and full consideration of Applicant's arguments, the specification lacks information to lead one of skill in the art to understand that the applicant had possession of the broadly claimed invention at the time the instant application was filed. Therefore, one of skill in the art would not understand that the applicant had possession of the claimed invention at the time the instant application was filed and this rejection is maintained.

17. The rejection of Claims 1-3, 6-19, 22, 24, 26, 27, 30-34 and 37 under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description, is maintained.

At page 37 of the amendment filed April 16, 2007, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but are not found persuasive for the following reasons:

Applicants submit that a copy of the deposit receipt and a signed statement of availability sufficient to overcome the rejection is attached.

In response the signed Statement of Availability is insufficient to overcome the rejection as it does not provide the assurances that the deposit will be replaced if viable samples cannot be dispensed by the depository and access to the deposit will be available during pendency of the patent application making reference to the deposit to one determined by the Commissioner to be entitled thereto under 37 CFR 1.14 and 35 U.S.C. 122 . This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves these specific matters to the discretion of each State.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

18. The rejection of Claims 1-3, 6-19, 22, 24, 26, 27, 30-34 and 37 under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making and using** a composition comprising an antibody or antibody fragment that specifically binds to an insulin-like growth factor-I receptor (IGF-I-R), wherein said antibody or antibody fragment comprises a heavy chain variable region comprising a CDR1 consisting of SEQ ID NO:1, a CDR2 consisting of SEQ ID NO:2, a CDR3 consisting of SEQ ID NO:3 and a light chain variable region comprising a CDR1 consisting of SEQ ID NO:4, a CDR2 consisting of SEQ ID NO:5, a CDR3 consisting of SEQ ID NO:6 or antibodies taught in the prior art

that specifically bind IGF-I-R, **does not reasonably provide enablement for making and using** a composition comprising (i) antibodies with the same binding specificity as murine antibody EM164 that do not comprise the amino acid sequence of the 6 CDRs of antibody EM164, wherein the CDRs consist of SEQ ID Nos:1-6. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

At page 37 of the amendment filed April 16, 2007, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

As set forth in the above rejection of the claims as lacking adequate written description, the claims are still being interpreted as drawn to functional equivalents or variants of antibodies that have the same binding specificity as murine antibody EM164, but do not require said antibody to comprise all 6 CDRs of the murine monoclonal antibody in their proper context, wherein the CDRs consist of SEQ ID Nos:1-6.

Applicant has argued that domain antibodies consisting of only variable heavy chain regions are known in the art citing the references of Holt et al, Aires da Silva et al, Tanaka et al and Peterson et al. In response to this argument, applicant appears to be relying on the cited art to enable functional equivalents of antibodies with the same binding specificity as the murine antibody EM164, yet the specification has not provided any specific, non-general guidance on how to

make such functional equivalents. The art cited by applicant is generally directed to domain antibodies from camelids, which have evolved to exist as single domain antibodies, whereas the instant specification discloses antibodies that naturally comprise a VH-VL pair. Therefore, it is apparent that undue experimentation would be required to make functional equivalents or variants of antibodies that have the same binding specificity as murine antibody EM164.

For example, as evidenced by Rudikoff et al (of record) and Watkins et al (of record), it is well established in the art that the formation of an intact antigen-binding site of antibodies that naturally comprise a VH-VL pair requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope. Notably, Watkins et al teach an antibody comprising a light chain (Vk domain of HUI77) that is 95% identical to SEQ ID NO:8 and the antibody binds collagen. Thus it is apparent that it is highly unpredictable which antigen an antibody will bind based on homology alone. Thus, while Applicants assert at page 38, last paragraph that changes to the light and heavy chain can be easily made without changing the specificity and point to paragraphs 68, 75-76 and 160-179 of the specification as enabling these changes, this argument is not persuasive as the specification does not provide specific, non-general guidance on how to make the antibodies encompassed by the claims. For example, the disclosure at paragraphs 68 and 160-179 teach methods of making humanized antibodies comprising resurfacing and CDR grafting of murine monoclonal antibodies and it is noted that such humanized or resurfaced antibodies comprise all 6 CDRs of the parent antibody in appropriate human heavy and light chain framework regions. Additionally, paragraphs 75-76 teach methods of screening for variants of a primary antibody by randomly changing the CDR sequences, but these paragraphs do not provide any specific guidance as to which CDR residues could be altered in the EM164 antibody to retain antigen binding. Accordingly undue and unreasonable experimentation would be required to

determine which residues could predictably be altered while retaining antigen binding.

Applicant is reminded that reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

Thus, the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to identify other antibodies that are encompassed by the claims; yet, defining a substance by its principal biological activity amounts to an alleged conception having no more specificity than that of a wish to know the identity of any material with that biological property. See *Colbert v. Lofdahl*, 21 USPQ2d 1068, 1071 (BPAI 1991).

In conclusion, upon careful consideration of Applicant's arguments and the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enabled the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC § 102

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

20. The rejection of Claims 1, 6, 19, 22, 24 and 26 under 35 U.S.C. 102(b) as being anticipated by Zia et al (Journal of Cellular Biochemistry Supplement 24:269-275, 1996, IDS filed August 03, 2005), is maintained.

At page 39 of the amendment filed April 16, 2007, Applicant has traversed this ground of rejection.

Applicant has argued that the insulin-like growth factor-I receptor antibody of Zia et al does not have the same binding specificity as the murine monoclonal antibody EM164 as it agonizes receptor function while the EM164 antibody does not.

In response, both antibodies bind to the same antigen, i.e, insulin-like growth factor-I receptor antibody and therefore the antibody of Zia et al is deemed to meet the limitation of having the same binding specificity, i.e, antigen-binding specificity, as the murine monoclonal antibody EM164. Notably, the claims do not require the antibodies to have any particular function except specific binding to insulin-like growth factor-I receptor. Additionally, in response to Applicant's assertion that the antibody of Zia et al does not inhibit the growth of lung cancer cells it is noted that the ^{125}I-αIR-3 is internalized into lung cancer cells (see e.g., page 271) and that the naked antibody inhibits lung cancer tumor growth both in vitro and in vivo (see e.g., abstract), so the IR-3 antibody conjugated to a cytotoxic agent that gets internalized into lung cancer cells would inherently inhibit lung cancer cell growth.

For these reasons, the Examiner disagrees with Applicant's contention that Zia et al no longer anticipate the instant claims and the rejection of claims 1, 6, 19, 22, 24 and 26 under 35 U.S.C. 102(b), as being anticipated by Zia et al, is maintained.

21. The rejection of Claims 1-3, 6-19, 22, 24, 26, 27, 30-34 and 37 under 35 U.S.C. 102(a) as being anticipated by Maloney et al (Cancer Research 63:5073-5083, August 15, 2003, IDS filed August 25, 2004), is maintained.

At page 42 of the amendment filed April 16, 2007, Applicant has traversed this ground of rejection.

Applicant has argued that the Declaration Under 37 CFR 1.132 is sufficient to overcome this rejection. However, as noted above, a factual error was noted in the first declaration filed April 16, 2007, and the copy of the declaration filed August 24, 2007 is not executed; accordingly, neither declaration is considered sufficient to overcome this ground of rejection.

Additionally, it is noted that Maloney et al teach a humanized version of the EM164 antibody (see e.g., page 5082, right column).

For these reasons, the Examiner disagrees with Applicant's contention that Maloney et al no longer anticipate the instant claims and the rejection of claims 1-3, 6-19, 22, 24, 26, 27, 30-34 and 37 under 35 U.S.C. 102(b), as being anticipated by Maloney et al, is maintained.

22. The rejection of Claims 1, 6, 19, 22, 24 and 26 under 35 U.S.C. 102(b) as being anticipated Rohlik et al (Biochemical and Biophysical Research Communications 149:276-281, November 30, 1987), is maintained.

At page 43 of the amendment filed April 16, 2007, Applicant has traversed this ground of rejection.

Applicant has argued that the insulin-like growth factor-I receptor antibody of Rohlik et al does not have the same binding specificity as the murine monoclonal antibody EM164 for essentially the same reasons as set forth to address the Zia et al 102 (b) rejection on page 39.

In response, both antibodies bind to the same antigen, i.e, insulin-like growth factor-I receptor antibody and therefore the antibody of Rohlik et al is deemed to meet the limitation of having the same binding specificity, i.e, antigen-binding specificity, as the murine monoclonal antibody EM164. Notably, the

claims do not require the antibodies to have any particular function except specific binding to insulin-like growth factor-I receptor.

For these reasons, the Examiner disagrees with Applicant's contention that Rohlik et al no longer anticipate the instant claims and the rejection of claims 1, 6, 19, 22, 24 and 26 under 35 U.S.C. 102(b), as being anticipated by Rohlik et al, is maintained.

Claim Rejections - 35 USC § 103

23. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

24. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of

35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

25. The rejection of claims 1-2 and 32 under 35 U.S.C. 103(a), as being unpatentable over Rohlik et al (Biochemical and Biophysical Research Communications 149:276-281, November 30, 1987), in view of Teicher et al (Clinical Cancer Research 5:2638-2645, September 1999), is maintained.

At page 43 of the amendment filed April 16, 2007, Applicant has traversed this ground of rejection.

In this traversal, Applicant has repeated the argument that the insulin-like growth factor-I receptor antibody of Rohlik et al does not have the same binding specificity as the murine monoclonal antibody EM164.

In response, both antibodies bind to the same antigen, i.e, insulin-like growth factor-I receptor antibody and therefore the antibody of Rohlik et al is deemed to meet the limitation of having the same binding specificity, i.e, antigen-binding specificity, as the murine monoclonal antibody EM164. Notably, the claims do not require the antibodies to have any particular function except specific binding to insulin-like growth factor-I receptor.

Furthermore, as set forth in the preceding Office action it would be obvious to combine the antibody of Rohlik with the bortezomib of Teicher et al as both agents are useful for the same purpose.

For these reasons, the Examiner disagrees with Applicant's contention that the rejection should be withdrawn and the rejection of claims 1-2 and 32 as being unpatentable over Rohlik et al in view of Teicher et al is maintained.

Double Patenting

26. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application

claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

27. The provisional rejection of Claims 1-3, 6-18, 32-33 and 37 on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-27 of copending Application No. 10/170,390 in view of Teicher et al, is maintained for the reasons of record, as explained in the previous Office action.

At page 44 of the amendment filed April 16, 2007, Applicant has noted that both Applications are currently pending and requested that the rejection be held in abeyance.

However, the pending claims have not been amended sufficiently to overcome this rejection and it will be maintained until it is appropriately resolved.

28. The provisional rejection of Claims 19, 22, 24, 26, 27, 30, 31 and 34 on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claim 30 of copending Application No. 10/170,390 in view of Teicher et al, is maintained for the reasons of record, as explained in the previous Office action.

At page 44 of the amendment filed April 16, 2007, Applicant has noted that both Applcaintion are currently pending and requested that the rejection be held in abeyance.

However, the pending claims have not been amended sufficiently to overcome this rejection and it will be maintained until it is appropriately resolved.

New Grounds of Objection

Specification

29. The amendment filed April 16, 2007 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the paragraphs added after paragraph 92 from the DeVita et al reference that occur on pages 2-9 of the amendment.

As noted in the preceding Office action at page 5, the DeVita et al incorporation by reference of the therapeutic agents thalidomide, carmustine, pamidronate, prednisone, erythropoietin and bisohosphonate was considered improper as these agents were considered essential material. Applicant did not point with any particularity to any disclosures in DeVita that recite these agents in the specification as *originally filed* and therefore amending the specification to include sections of DeVita that were not specifically identified in the specification as *originally filed*, while excluding other sections is deemed to introduce new matter into the disclosure of the invention.

Applicant is required to cancel the new matter in the reply to this Office Action.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

30. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

31. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

32. Claims 1 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zia et al (Journal of Cellular Biochemistry Supplement 24:269-275, 1996, IDS filed August 03, 2005), in view of Queen et al (U.S. Patent 5,530,101, 6/25/1996, IDS filed August 03, 2005).

Claims 1 and 37 are herein drawn to compositions comprising humanized antibodies that bind to insulin-like growth factor-I receptor with the same specificity as murine antibody EM164, including functional equivalents of the EM164 antibody.

Support for this interpretation occurs in original claim 1 that discloses functional equivalents of an antibody having the same binding specificity as

murine antibody EM164 and in the specification at page 19 that discloses: "The invention also includes functional equivalents of the antibodies described in this specification. Functional equivalents have binding characteristics that are comparable to those of the antibodies".

Zia et al teach the murine monoclonal antibody IR-3 that specifically binds to insulin-like growth factor-I receptor and is being considered a functional equivalent of murine antibody EM164 since it has the same binding specificity as EM164 (see whole document, e.g., page 270). Zia et al also teach conjugating αIR-3 to ^{125}I, wherein ^{125}I is considered a second agent (e.g., abstract) and that the IR-3 antibody inhibits tumor lung tumor growth in a mouse model. Zia et al do not expressly teach humanizing the IR-3 antibody. This deficiency is made up for in the teachings of Queen et al.

Queen et al teach methods of humanizing murine monoclonal antibodies for human therapy and that such antibodies have advantages in being less immunogenic in humans (see entire document, e.g., columns 1 and 19-20).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to humanize the IR-3 antibody of Zia et al in view of Queen et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention to humanize the IR-3 antibody of Zia et al as Queen teach methods of humanizing murine monoclonal antibodies and that such antibodies have advantages over the murine antibody in therapy. Furthermore, since Zia et al teach that the murine monoclonal antibody IR-3 inhibits growth of lung cancer cells, one of skill in the art would have been further motivated to humanize it. Thus, there would be an advantage and a reasonable expectation of success in humanizing the murine monoclonal antibody IR-3 of Zia et al and conjugating it to ^{125}I in view of Queen et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

33. Claims 1 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rohlik et al (Biochemical and Biophysical Research Communications 149:276-281, November 30, 1987), in view of Queen et al (U.S. Patent 5,530,101, 6/25/1996, IDS filed August 03, 2005).

Claims 1 and 37 are herein drawn to compositions comprising humanized antibodies that bind to insulin-like growth factor-I receptor with the same specificity as murine antibody EM164, including functional equivalents the EM164 antibody.

Again, support for this interpretation occurs in original claim 1 that discloses functional equivalents of an antibody having the same binding specificity as murine antibody EM164 and in the specification at page 19 that discloses: "The invention also includes functional equivalents of the antibodies described in this specification. Functional equivalents have binding characteristics that are comparable to those of the antibodies".

Rohlik et al teach the murine monoclonal antibody, alpha IR-3 that specifically binds to the insulin-like growth factor I receptor and is being considered a functional equivalent of murine antibody EM164 since it has the same binding specificity as EM164 (see entire document, e.g., page 276, first paragraph). Furthermore, Rohlik et al teach αIR-3 in a composition with ^{125}I-insulin-like growth factor I and that such a composition inhibits the growth of the breast cancer cell line, MCF-7 (e.g., figure 1 and 2). Rohlik et al do not expressly teach humanizing the IR-3 antibody. This deficiency is made up for in the teachings of Queen et al.

Queen et al teach methods of humanizing murine monoclonal antibodies for human therapy and that such antibodies have advantages in being less immunogenic in humans (see entire document, e.g., columns 1 and 19-20).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to humanize the IR-3 antibody of Rohlik et al in view of Queen et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention to humanize the IR-3 antibody of Rohlik et al as Queen teach methods of humanizing murine monoclonal antibodies and that such antibodies have advantages over the murine antibody in therapy. Furthermore, since Rohlik et al teach that the murine monoclonal antibody IR-3 inhibits the growth of the breast cancer cell line, MCF-7 in a composition with ^{125}I-insulin-like growth factor I, one of skill in the art would have been further motivated to humanize it. Thus, there would be an advantage and a reasonable expectation of success in humanizing the murine monoclonal antibody IR-3 of Rohlik et al and including it in a composition with ^{125}I-insulin-like growth factor I in view of Queen et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

34. No claim is allowed.

35. Applicant's amendment necessitated the new ground(s) of objection and rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

35. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Friday 7:00 AM to 4:30 PM, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
571-272-9935

/Stephen L. Rawlings/
Stephen L. Rawlings, Ph.D.
Primary Examiner, Art Unit 1643

bd
September 17, 2007